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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/628,792	07/28/2003	Jon A. Wolff	Mirus.040.01	5528

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EXAMINER	
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1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/628,792	WOLFF ET AL.	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-30* is/are pending in the application.

4a) Of the above claim(s) *11, 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10,12-27,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after Non-final rejection filed on November 06, 2007 is acknowledged. Claims 1-30 are pending in this application. Applicant elected Group 1 (claims 9-10) drawn to a process for delivering a molecule to an extravascular cell in a mammalian tissue wherein the molecule consists of protein/peptide and the election of hypertonic solution in the reply filed on July 02, 2007. The Applicant did not distinctly and specifically points out the supposed errors in the restriction requirement, the election was treated as an election without traverse. Therefore, the Restriction requirement was deemed proper and made FINAL. Claims 11 and 28 remain withdrawn from further consideration as being drawn to nonelected invention and species. Claims 1-2, 4-10, 12-26, 29 and 30 are examined on the merits in this office action.

Withdrawn Objections and Rejections

1. Objection to the title is hereby withdrawn due to Applicant's arguments.

2. Rejection under 35 U.S.C. 112, 2nd paragraph is hereby withdrawn due to Applicant's amendments and arguments.

New Rejection

35 U.S.C. 112, 1st

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-2, 4-8, 12-27 and 29-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

4. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the

claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

5. Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

6. The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court

determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

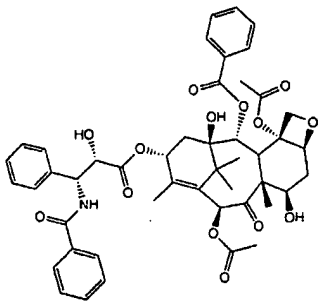
7. In the instant case, the claims are drawn to process for delivering a molecule to an extravascular cell in a mammalian target tissue in vivo. The generic statements molecule and protein and peptide do not provide ample written description for the compounds since the claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

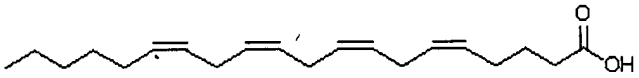
8. As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claims 1 and 9-10 are broad generics with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of molecules, cells, agonists, antagonists, synthetic and natural molecules, peptide or a peptide-like molecule, and other compounds such as DNA, RNA, siRNA. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to

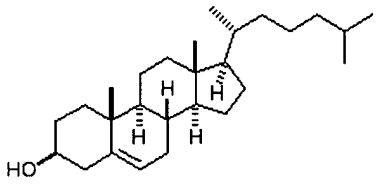
reflect this variance in the genus since the specification does not provide any examples of derivatives, homologs or variants. The specification is void of organic molecules that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a peptide or a peptide-like molecule. The specification is also void of other molecules such as cells, chemical molecules, vitamins, amino acids, salts, sugars, any other organic molecules, natural products such as taxol, cholesterol, steroids, and any other molecules that are biologically active.

9. The specification is limited to the nucleic acid, protein and therapeutic compound, and the molecule can be neutral, cationic or anionic (see paragraph [0013]). The specification defines biologically active compound as a compound having the potential to react with biological components. The biologically active compounds may be selected from the list comprising pharmaceuticals, proteins, peptides, polypeptides, enzyme inhibitors, hormones, cytokines, antigens, viruses, oligonucleotide, enzymes and nucleic acid (see paragraph [0067]). Claim 4 recites that the molecule consists of a biologically active compound. However, the pharmaceuticals, proteins, peptides, polypeptides, enzymes inhibitors are not fully defined and the genus has a substantial variance. For example, proteins or peptides have structural differences due to amino acid content. There are 20 naturally occurring amino acids, and non-natural amino acids, such as D-amino acids, β-amino acids, γ-amino acids, ε-amino acids, and amino acid mimetics that can form peptide bonds to make up a peptide, protein, or polypeptides. Additionally, there are synthetic organic small molecules that also mimic peptides. Therefore, the numbers of peptide, protein, and polypeptides are innumerable. The specification lists

dextran, immunoglobulin, streptavidin-NLS protein, galactosidase, polystyrene, BOBO-3 nucleic acid stain, SV40 NLS peptide (SEQ ID NO: 1), anti-NUP62 monoclonal IgG, and T7 20-6 phage (see paragraphs [0245]-[0254]). The working examples only describe the dextran, immunoglobulin, streptavidin-NLS protein, galactosidase, polystyrene, BOBO-3 nucleic acid stain, SV40 NLS peptide (SEQ ID NO: 1), anti-NUP62 monoclonal IgG, and T7 20-6 phage. The specification does not describe any other enzymes, any other peptide, polypeptides, proteins, antibodies, pharmaceuticals, cytokines, DNA, RNA, viral vectors and other plasmids, any other synthetic molecules comprising repeating polypeptide units or any other proteins in plants, vegetables and meat (such as hemoglobin, collagen, gelatin, etc). Description of dextran, immunoglobulin, streptavidin-NLS protein, galactosidase, polystyrene, BOBO-3 nucleic acid stain, SV40 NLS peptide (SEQ ID NO: 1), anti-NUP62 monoclonal IgG, and T7 20-6 phage is not sufficient to encompass numerous other molecules that belong to the same genus. For example, as described above, for peptides and proteins, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. Additionally, possible polynucleotides, such as DNA and RNA, are also innumerable, since DNA, RNA make up are different and they encode and express different proteins. Molecules such as organic compounds (for example, pharmaceutical compounds) are also innumerable, since they are structurally different. For example,

Taxol (a naturally occurring molecule) has the structure 

while arachidonic acid has the structure 

and cholesterol the structure  . There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

10. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Rejection-35 U.S.C. 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-10, 12-27 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Twist et al (US Patent # 5633230).

13. The instant claims are drawn to a process for delivering a molecule, and the active steps of the process is inserting an injection solution containing the molecule into the lumen of an efferent or afferent vessel of the target tissue.

14. Twist et al teach the assessment of peptide distribution, in vivo. The distribution and localization of a ^{14}C-acetyl form of peptide AV9 was determined following administration by intravenous and sub-cutaneous injection dissolved in 10 mL PBS. The reference teaches that both i.v. and s.c. injection brought about rapid distribution of drug to tissues. The highest and most prolonged levels are attained in the liver, followed by the kidneys and spleen (see Example 4). Since the active steps of the process are disclosed in Twist patent '230, and the subsequent claims do not alter the active step of the process, Twist reference meets the limitations of claims 1-10, 12-27 and 29.

15. Claims 1-10, 12-27, 29 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Goddard et al (US Patent # 5602094).

16. The instant claims are drawn to a process for delivering a molecule, and the active steps of the process is inserting an injection solution containing the molecule into the lumen of an efferent or afferent vessel of the target tissue. Claim 30 recites the rapid insertion of a sufficient volume of injection solution.

17. Goddard et al teach the treatment of tumors by administration of PLAP peptide. The reference teaches that two groups of 12 rats were injected with the PLAP and with agarose beads alone (as control). In order to ensure uniform distribution of the bound peptide, the total volumes were increased to 10 ml by the addition of 6 ml sterile saline solution immediately prior to injection. The reference teaches that 72 hours after injection, the rats were euthanized and tumor effusions were aspirated (see column 4, lines 25-45). Since the active steps of the process are disclosed in Goddard patent '094, and the subsequent claims do not alter the active step of the process, Goddard reference meets the limitations of claims 1-10, 12-27, 29 and 30.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

18. Claims 1-2, 4-8, 12-27, 29 and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by Woiff et al (PG Pub 2002/0001574 A1).

19. The instant claims are drawn to a process for delivering a molecule, and the active steps of the process is inserting an injection solution containing the molecule into the lumen of an efferent or afferent vessel of the target tissue.

20. Woiff et al teach process of delivering a polynucleotide to a muscle cell via the vascular system (see title). The reference teaches a process for delivering a coded polynucleotide into a parenchymal cell of a mammal for expression of a protein, comprising, transporting the polynucleotide to a vessel containing a fluid and having a permeable wall, and increasing the permeability of the wall for a time sufficient to complete delivery of the polynucleotide (see paragraph [0011]). This reads on claims 1, 4-5, 12-14 and 30. The reference teaches that a polynucleotide can be delivered to a cell in order to produce a cellular change that is therapeutic...the polynucleotides coded to express a whole or partial protein (see paragraph [0020]). The reference further teaches that the permeability of a blood vessel can be increased by increasing the intravascular hydrostatic pressure...hydrostatic pressure is increased by rapidly injecting a polynucleotide in solution into the blood vessel which increases the hydrostatic pressure (see paragraph [0045]). This further reads on claim 30. Further, the reference teaches that in the liver, the hepatic vein is an efferent blood vessel, and portal vein and hepatic arteries are afferent blood vessels...and in some of the animals that received retrograde injections in the inferior vena cava, the hepatic artery, mesenteric artery and portal vein were clamped (occluded) (see paragraph [0043])...the permeability of a blood vessel can be increased by increasing the intravascular hydrostatic pressure...an afferent vessel supplying an organ is rapidly injected and the

efferent vessel draining the tissue is ligated transiently. The efferent vessel draining outflow from the tissue is also partially or totally clamped for a period of time sufficient to allow delivery of a polynucleotide. In reverse, an efferent is injected and an afferent vessel is occluded (see paragraph [0045]). This reads on claim 2 and 16-24. The reference teaches that typically, hypertonic solutions containing salts such as NaCl, sugars or polyols such as mannitol are used. Hypertonic means that the osmolality of the injection solution is greater than physiologic osmolality...hypertonic solutions have increased tonicity and osmotic pressure similar to the osmotic pressure similar to the osmotic pressure of blood and cause cells to shrink (see paragraph [0046]). The reference shows examples of injection and expression in rat hind limb muscles (see paragraph [0016])...in striated muscle, the parenchymal cells include myoblasts...in cardiac muscle, the parenchymal cells include the myocardium also known as cardiac muscle fibers or cardiac muscle cells (see paragraph [0026]). This reads on claims 18 and 19. The reference further teaches that the expression of a foreign DNA was obtained in mammalian liver by intraportally injecting plasmid DNA in a hypertonic solution and transiently clamping the hepatic vein/inferior vena cave. Optimal expression was obtained by clamping the portal vein and injecting the hepatic vein/inferior vena cava (see paragraph [0009]). This reads on claim 29. Since the reference teaches polynucleotide is naked DNA (not associated with a transfection reagent or other delivery vehicle (see paragraph [0018]), and assuming about 330 daltons per nucleotide, this implies for a pair of nucleotide, the molecular weight is 660 daltons. Therefore, this meets the limitations of claims 6-8. Additionally, since all of the

active steps are disclosed in Woiff et al reference, and the subsequent claims do not alter the active step of the process, Woiff reference meets the limitations of claims 1-2, 4-8, 12-27, 29 and 30. Please note that the reference also teaches hypotonic solution, the nonelected species.

21. Claims 1-2, 4-8, 12-27, 29 and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by Woiff et al (PG Pub 2002/0001574 A1).

22. The instant claims are described above.

23. The teachings of Woiff et al are described above.

Obviousness Double Patenting

24. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

25. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

26. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

27. Claims 1-2, 4-8, 12-14, 16-17, 23, 29 and 30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12, and 14 of U.S. Patent No. 7144869. Although the conflicting claims are not identical, they are not patentably distinct from each other because if one practiced the claimed invention of the instant application, one would necessarily achieve the claimed invention of U.S. Patent '869.

28. The instant claims are drawn to a process for delivering a molecule to an extravascular cell in a mammalian target tissue (liver cell, hepatocyte) in vivo and blood vessel consists of a vein.

29. The claims of U.S. Patent '869 are drawn to a process for delivering a polynucleotide to a primate liver cell, comprising a) transiently occluding afferent and efferent blood vessels of the liver in a primate; and b) injecting the polynucleotide in a solution into the lumen of a hepatic Bessel wherein the injection of the solution results in portal vein pressure of 10 mm Hg or greater (see claims 1-11). Claim 7 recites that the polynucleotide consists of naked DNA (not associated with a transfection reagent or other delivery vehicle). Claims 12 and 14 are further drawn to the hepatic vessel consists of hepatic vein and portal vein. Assuming about 330 daltons per nucleotide, this implies that for a pair of nucleotide, the molecular weight is 660 daltons. The molecular weight of the DNA would depend on the size of the DNA.

30. Therefore, if one of ordinary skill in the art practiced the claimed invention of instant application, one would necessarily achieve the claimed invention of the patented claims of '869 and vice versa.

Conclusion

30. No claims are allowed.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

32. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

32. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Julie Ha
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AU 1654

1/4/07
ANISH GUPTA
PRIMARY EXAMINER